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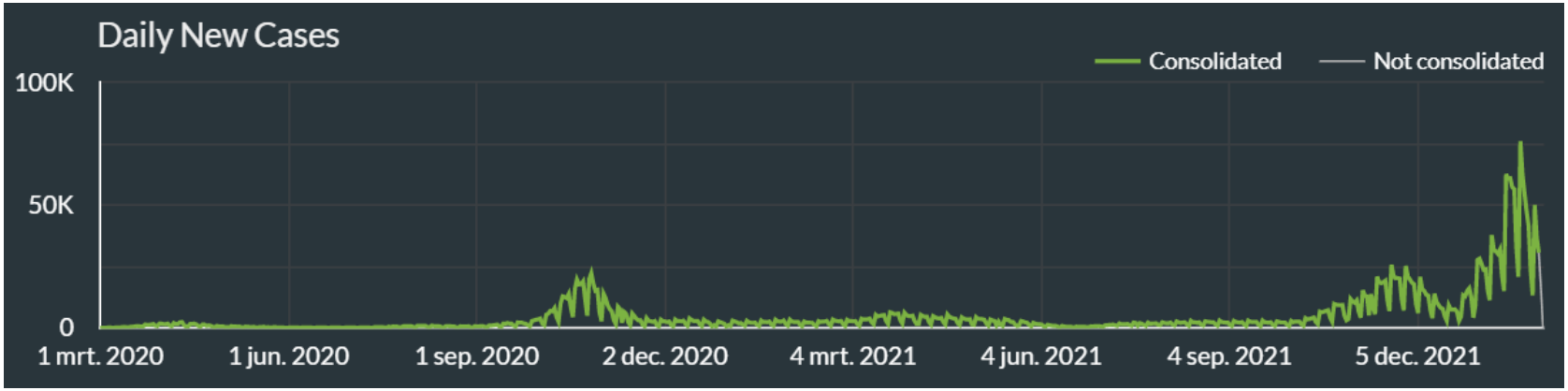
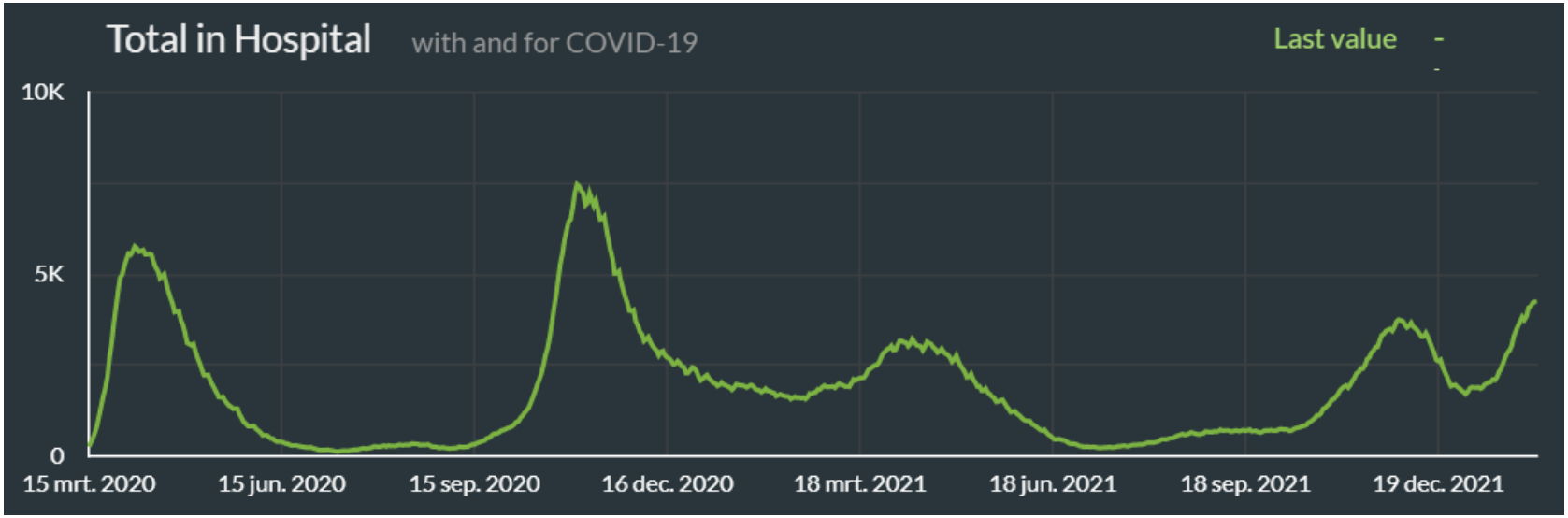
Scientific News
6th of February 2022
Sven Bulterijs

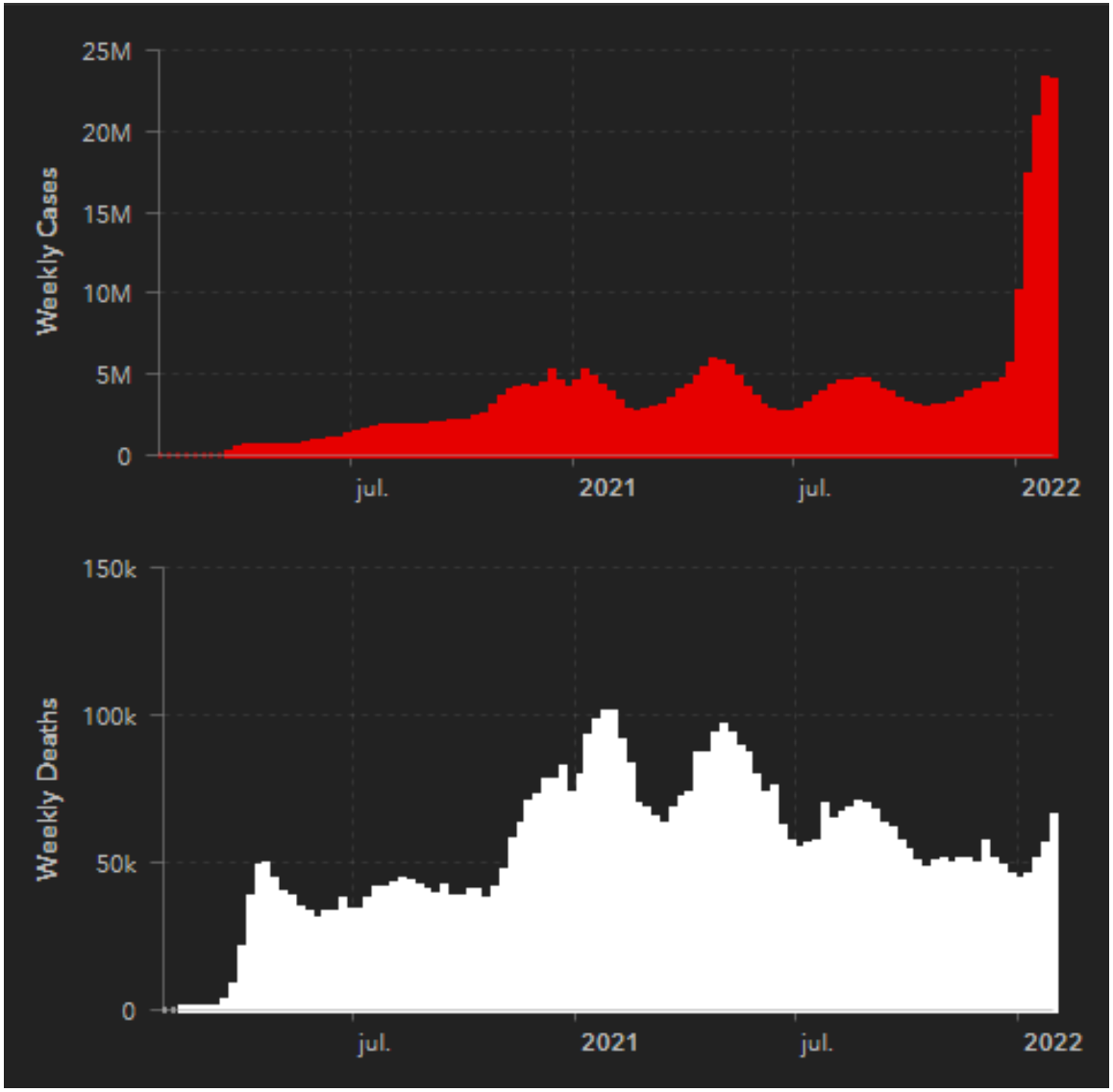
Business/Conferences/ General news

Belgium





World



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WORLD VIEW | 24 January 2022

COVID-19: endemic doesn't mean harmless

Rosy assumptions endanger public health — policymakers must act now to shape the years to come.

Aris Katzourakis

The word 'endemic' has become one of the most misused of the pandemic. And many of the errant assumptions made encourage a misplaced complacency. It doesn't mean that COVID-19 will come to a natural end.

To an epidemiologist, an endemic infection is one in which overall rates are static — not rising, not falling. More precisely, it means that the proportion of people who can get sick balances out the 'basic reproduction number' of the virus, the number of individuals that an infected individual would infect, assuming a population in which everyone could get sick. Yes, common colds are endemic. So are Lassa fever, malaria and polio. So was smallpox, until vaccines stamped it out.

In other words, a disease can be endemic and both widespread and deadly. Malaria killed more than 600,000 people in 2020. Ten million fell ill with tuberculosis that same year and 1.5 million died. Endemic certainly does not mean that evolution has somehow tamed a pathogen so that life simply returns to 'normal'.

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The pandemic's true death toll: millions more than official counts

Countries have reported some five million COVID-19 deaths in two years, but global excess deaths are estimated at double or even quadruple that figure.

David Adam

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Tracking cryptic SARS-CoV-2 lineages detected in NYC wastewater

Davida S. Smyth, Monica Trujillo, Devon A. Gregory, Kristen Cheung, Anna Gao, Maddie Graham, Yue Guan, Caitlyn Guldenpfennig, Irene Hoxie, Sherin Kannoly, Nanami Kubota, Terri D. Lyddon, Michelle Markman, Clayton Rushford, Kaung Myat San, Geena Sompanya, Fabrizio Spagnolo, Reinier Suarez, Emma Teixeiro, Mark Daniels, Marc C. Johnson ✉ & John J. Dennehy ✉

Nature Communications **13**, Article number: 635 (2022) | Cite this article

Abstract

Tracking SARS-CoV-2 genetic diversity is strongly indicated because diversifying selection may lead to the emergence of novel variants resistant to naturally acquired or vaccine-induced immunity. To monitor New York City (NYC) for the presence of novel variants, we deep sequence most of the receptor binding domain coding sequence of the S protein of SARS-CoV-2 isolated from the New York City wastewater. Here we report detecting increasing frequencies of novel cryptic SARS-CoV-2 lineages not recognized in GISAID's EpiCoV database. These lineages contain mutations that had been rarely observed in clinical samples, including Q493K, Q498Y, E484A, and T572N and share many mutations with the Omicron variant of concern. Some of these mutations expand the tropism of SARS-CoV-2 pseudoviruses by allowing infection of cells expressing the human, mouse, or rat ACE2 receptor. Finally, pseudoviruses containing the spike amino acid sequence of these lineages were resistant to different classes of receptor binding domain neutralizing monoclonal antibodies. We offer several hypotheses for the anomalous presence of these lineages, including the possibility that these lineages are derived from unsampled human COVID-19 infections or that they indicate the presence of a non-human animal reservoir.

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PREPRINT

The Dynamics of SARS-CoV-2 Infectivity with Changes in Aerosol Microenvironment

Henry P. Oswin[1], Allen E. Haddrell[1]*, Mara Otero-Fernandez[1], Jamie F.S. Mann[2], Tristan A. Cogan[2], Tom Hilditch[1], Jianghan Tian[1], Dan Hardy[1], Darryl J. Hill[3], Adam Finn[3], Andrew D. Davidson[3]*, and Jonathan P. Reid[1]*

Understanding the factors that influence the airborne survival of viruses such as SARS-CoV-2 in aerosols is important for identifying routes of transmission and the value of various mitigation strategies for preventing transmission. We present measurements of the stability of SARS-CoV-2 in aerosol droplets (~5-10μm equilibrated radius) over timescales spanning from 5 seconds to 20 minutes using a novel instrument to probe survival in a small population of droplets (typically 5-10) containing ~1 virus/droplet. Measurements of airborne infectivity change are coupled with a detailed physicochemical analysis of the airborne droplets containing the virus. A decrease in infectivity to ~10 % of the starting value was observable for SARS-CoV-2 over 20 minutes, with a large proportion of the loss occurring within the first 5 minutes after aerosolisation. The initial rate of infectivity loss was found to correlate with physical transformation of the equilibrating droplet; salts within the droplets crystallise at RHs below 50% leading to a near instant loss of infectivity in 50–60% of the virus. However, at 90% RH the droplet remains homogenous and aqueous, and the viral stability is sustained for the first 2 minutes, beyond which it decays to only 10% remaining infectious after 10 minutes. The loss of infectivity at high RH is consistent with an elevation in the pH of the droplets, caused by volatilisation of CO_2 from bicarbonate buffer within the droplet. Three different variants of SARS-CoV-2 were compared and found to have a similar degree of airborne stability at both high and low RH.

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First pig-to-human heart transplant: what can scientists learn?

Researchers hope that a person who has so far lived for a week with a genetically modified pig heart will provide a trove of data on the possibilities of xenotransplantation.

Sara Reardon

Surgeons at the University of Maryland Medical Center transplanted a genetically altered pig heart into

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Source: Photo by Rod Long on Unsplash

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ALTOS

- **Focus: cellular rejuvenation**
- **Funding: $3 billion**
- **Main investor: Jeff Bezos**
- **CEO: Hal Barron**
- **Board: Jennifer Doudna, Frances Arnold, David Baltimore**
- **Senior scientific advisor: Shinya Yamanaka**
- **Researchers: Juan Carlos Izpisua Belmonte, Morgan Levine, Steven Horvath,…**
- **3 institutes: San Francisco Bay Area and San Diego (US), Cambridge (UK), with additional significant collaborations in Japan**

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Tech entrepreneurs pledge $2.5 million to Dog Aging Project

Support will expand research on interventions to increase healthy years of life

MEDIA CONTACT: Leila Gray, 206.475.9809, leilag@uw.edu

Dog Aging Project

Zoe, one of the participants in the Dog Aging Project, with her owner.

The Dog Aging Project, a scientific initiative to help companion dogs and people live longer, healthier lives together, has received a $2.5 million pledge from a consortium of tech entrepreneurs.

The Dog Aging Project brings together a community of dogs, owners, veterinarians, researchers, and volunteers to carry out the largest canine health study in the world. The donation will expand this research into longevity science.

The donors include Brian Armstrong, Coinbase founder and CEO; Peter Attia, physician; Juan Benet, Protocol Labs founder and CEO; Fred Erhsam, co-founder of Paradigm and Coinbase; Adam Fisher of Bessemer Venture Partners; author Tim Ferriss and the Saisei Foundation; Jed McCaleb, Stellar co-founder and CTO and founder of the Astera Institute; and food author Darya Rose and internet entrepreneur Kevin Rose.

Aging research articles

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Naked mole-rats maintain cardiac function and body composition well into their fourth decade of life

Emine Can, Megan Smith, Bastiaan J. Boukens, Ruben Coronel, Rochelle Buffenstein ✉ & Johannes Riegler ✉

GeroScience (2022) | Cite this article

The prevalence of cardiovascular disease increases exponentially with age, highlighting the contribution of aging mechanisms to cardiac diseases. Although model organisms which share human disease pathologies can elucidate mechanisms driving disease, they do not provide us with innate examples how cardiac aging might be slowed or attenuated. The identification of animal models that preserve cardiac function throughout most of life offers an alternative approach to study mechanisms which might slow cardiac aging. One such species may be the naked mole-rat (NMR), a mouse-sized (40 g) rodent with extraordinary longevity (> 37 years), and constant mortality hazard over its four decades of life. We used a cross-sectional study design to measure a range of physiological parameters in NMRs between 2 and 34 years of age and compared these findings with those of mice aged between 3 months and 2.5 years. We observed a rapid decline in body fat content and bone mineral density in old mice, but no changes in NMRs. Similarly, rhythm disorders (premature atrial and ventricular complexes) occurred in aged mice but not in NMRs. Magnetic resonance and ultrasound imaging showed age-dependent increases in cardiac hypertrophy and diastolic dysfunction in mice which were absent in NMRs. Finally, cardiac stress tests showed an age-dependent decline in normalized cardiac output in mice, which was absent in NMRs. Unlike mice, that manifest several aspects of human cardiac aging, NMRs maintain cardiac function and reserve capacity throughout their long lives and may offer insights on how to delay or prevent cardiac aging.

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Ageing exacerbates ribosome pausing to disrupt cotranslational proteostasis

Kevin C. Stein, Fabián Morales-Polanco, Joris van der Lienden, T. Kelly Rainbolt & Judith Frydman

Nature **601**, 637–642 (2022) | Cite this article

13k Accesses | **223** Altmetric | Metrics

Abstract

Ageing is accompanied by a decline in cellular proteostasis, which underlies many age-related protein misfolding diseases[1,2]. Yet, how ageing impairs proteostasis remains unclear. As nascent polypeptides represent a substantial burden on the proteostasis network[3], we hypothesized that altered translational efficiency during ageing could help to drive the collapse of proteostasis. Here we show that ageing alters the kinetics of translation elongation in both *Caenorhabditis elegans* and *Saccharomyces cerevisiae*. Ribosome pausing was exacerbated at specific positions in aged yeast and worms, including polybasic stretches, leading to increased ribosome collisions known to trigger ribosome-associated quality control (RQC)[4,5,6]. Notably, aged yeast cells exhibited impaired clearance and increased aggregation of RQC substrates, indicating that ageing overwhelms this pathway. Indeed, long-lived yeast mutants reduced age-dependent ribosome pausing, and extended lifespan correlated with greater flux through the RQC pathway. Further linking altered translation to proteostasis collapse, we found that nascent polypeptides exhibiting age-dependent ribosome pausing in *C. elegans* were strongly enriched among age-dependent protein aggregates. Notably, ageing increased the pausing and aggregation of many components of proteostasis, which could initiate a cycle of proteostasis collapse. We propose that increased ribosome pausing, leading to RQC overload and nascent polypeptide aggregation, critically contributes to proteostasis impairment and systemic decline during ageing.

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Mendelian randomization of genetically independent aging phenotypes identifies LPA and VCAM1 as biological targets for human aging

Paul R. H. J. Timmers, Evgeny S. Tiys, Saori Sakaue, Masato Akiyama, Tuomo T. J. Kiiskinen, Wei Zhou, Shih-Jen Hwang, Chen Yao, Biobank Japan Project, FinnGen, Joris Deelen, Daniel Levy, Andrea Ganna, Yoichiro Kamatani, Yukinori Okada, Peter K. Joshi, James F. Wilson & Yakov A. Tsepilov

Nature Aging **2**, 19–30 (2022) | Cite this article

6980 Accesses | **1** Citations | **291** Altmetric | Metrics

Abstract

Length and quality of life are important to us all, yet identification of promising drug targets for human aging using genetics has had limited success. In the present study, we combine six European-ancestry genome-wide association studies of human aging traits—healthspan, father and mother lifespan, exceptional longevity, frailty index and self-rated health—in a principal component framework that maximizes their shared genetic architecture. The first principal component (aging-GIP1) captures both length of life and indices of mental and physical wellbeing. We identify 27 genomic regions associated with aging-GIP1, and provide additional, independent evidence for an effect on human aging for loci near *HTT* and *MAML3* using a study of Finnish and Japanese survival. Using proteome-wide, two-sample, Mendelian randomization and colocalization, we provide robust evidence for a detrimental effect of blood levels of apolipoprotein(a) and vascular cell adhesion molecule 1 on aging-GIP1. Together, our results demonstrate that combining multiple aging traits using genetic principal components enhances the power to detect biological targets for human aging.

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PREPRINT

Multi-omic rejuvenation of naturally aged tissues by a single cycle of transient reprogramming

Dafni Chondronasiou, Diljeet Gill, Lluc Mosteiro, Rocio G. Urdinguio, Antonio Berenguer, Monica Aguilera, Sylvere Durand, Fanny Aprahamian, Nitharsshini Nirmalathasan, Maria Abad, Daniel E. Martin-Herranz, Camille Stephan Otto-Attolini, Neus Prats, Guido Kroemer, Mario F. Fraga, Wolf Reik, Manuel Serrano

doi: https://doi.org/10.1101/2022.01.20.477063

ABSTRACT

The expression of the pluripotency factors OCT4, SOX2, KLF4 and MYC (OSKM) can convert somatic differentiated cells into pluripotent stem cells in a process known as reprogramming. Notably, cycles of brief OSKM expression do not change cell identity but can reverse markers of aging in cells and extend longevity in progeroid mice. However, little is known about the mechanisms involved. Here, we have studied changes in the DNA methylome, transcriptome and metabolome in naturally aged mice subject to a single period of transient OSKM expression. We found that this is sufficient to reverse DNA methylation changes that occur upon aging in the pancreas, liver, spleen and blood. Similarly, we observed reversion of transcriptional changes, especially regarding biological processes known to change during aging. Finally, some serum metabolites altered with aging were also restored to young levels upon transient reprogramming. These observations indicate that a single period of OSKM expression can drive epigenetic, transcriptomic and metabolomic changes towards a younger configuration in multiple tissues and in the serum.

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PREPRINT

Heterochronic parabiosis reprograms the mouse brain transcriptome by shifting aging signatures in multiple cell types

Methodios Ximerakis, Kristina M. Holton, Richard M. Giadone, Ceren Ozek, Monika Saxena, Samara Santiago, Xian Adiconis, Danielle Dionne, Lan Nguyen, Kavya M. Shah, Jill M. Goldstein, Caterina Gasperini, Scott L. Lipnick, Sean K. Simmons, Sean M. Buchanan, Amy J. Wagers, Aviv Regev, Joshua Z. Levin, Lee L. Rubin

doi: https://doi.org/10.1101/2022.01.27.477911

Abstract

Aging is a complex process involving transcriptomic changes associated with deterioration across multiple tissues and organs, including the brain. Recent studies using heterochronic parabiosis have shown that various aspects of aging-associated decline are modifiable or even reversible. To better understand how this occurs, we performed single-cell transcriptomic profiling of young and old mouse brains following parabiosis. For each cell type, we catalogued alterations in gene expression, molecular pathways, transcriptional networks, ligand-receptor interactions, and senescence status. Our analyses identified gene signatures demonstrating that heterochronic parabiosis regulates several hallmarks of aging in a cell-type-specific manner. Brain endothelial cells were found to be especially malleable to this intervention, exhibiting dynamic transcriptional changes that affect vascular structure and function. These findings suggest novel strategies for slowing deterioration and driving regeneration in the aging brain through approaches that do not rely on disease-specific mechanisms or actions of individual circulating factors.

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PREPRINT

Small extracellular vesicles from young mice prevent frailty, improve healthspan and decrease epigenetic age in old mice

Jorge Sanz-Ros, Cristina Mas-Bargues, Daniel Monleón, Juozas Gordevicius, Robert T. Brooke, Mar Dromant, Aksinya Derevyanko, Ana Guío-Carrión, Aurora Román-Domínguez, Nekane Romero-García, Marta Inglés, María A. Blasco, Steve Horvath, Jose Viña, Consuelo Borrás

doi: https://doi.org/10.1101/2021.07.29.454302

Summary

Aging is associated with an increased risk of frailty, disability, comorbidities, institutionalization, falls, fractures, hospitalization, and mortality. Searching for strategies to delay the degenerative changes associated with aging and frailty is interesting. We treated old animals intravenously with small extracellular vesicles (sEVs) derived from adipose mesenchymal stem cells (ADSCs) of young animals, and we found an improvement of several functional parameters usually altered with aging, such as motor coordination, grip strength, fatigue resistance, fur regeneration, and renal function. Frailty index analysis showed that 40% of old control mice were frail, whereas none of the old ADSCs-sEVs treated mice were. Molecular and structural benefits in muscle and kidney accompanied this functional improvement. ADSCs-sEVs induced pro-regenerative effects and a decrease in oxidative stress, inflammation, and senescence markers. Moreover, predicted epigenetic age was lower in tissues of old mice treated with ADSCs-sEVs and their metabolome changed to a youth-like pattern. Finally, we gained some insight into the miRNAs contained in sEVs that might be, at least in part, responsible for the effects observed. We propose that young sEVs treatment can be beneficial against frailty and therefore can promote healthy aging.

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Preclinical frailty assessments: Phenotype and frailty index identify frailty in different mice and are variably affected by chronic medications

Use of different objective frailty assessment tools may improve understanding of the biology of frailty and allow evaluation of effects of interventions on frailty. Polypharmacy is associated with increased risk of frailty in epidemiologic studies, regardless of frailty definition, but the pathophysiology of the association is not well understood. This study aims to (1) assess and compare the prevalence of frailty from middle to old age following control, chronic polypharmacy or monotherapy treatment, when measured using the clinical frailty index assessment and the mouse frailty phenotype tools; and (2) to evaluate and compare the effects of chronic polypharmacy regimens with zero, low and high Drug Burden Index (DBI) and monotherapies from middle to old age on the rate of deficit accumulation on the frailty index, mean number of phenotype criteria, odds of being frail assessed by the frailty index or phenotype, and the time to onset of frailty assessed by the frailty index or phenotype. In a longitudinal study, middle-aged (12 months) male C57BL/6J(B6) mice were administered non medicated control feed and water, or therapeutic doses of different polypharmacy combinations or monotherapies in feed and/or water. Frailty assessments were performed at 12, 15, 18, 21 and 24 months. There was limited overlap between animals identified as frail using different frailty assessments. Polypharmacy has measurable and different effects on each frailty assessment. Long-term chronic administration of some polypharmacy and monotherapy therapeutic drug regimens increased the number of frailty deficits (clinical frailty index: low DBI polypharmacy (15 and 21 months), high DBI polypharmacy (15–21 months), oxycodone (15–18 months), oxybutynin (15–18 months), citalopram (15–21 months) and metoprolol monotherapy (15 months) and modified frailty phenotype assessment (over the whole duration of treatment, low DBI polypharmacy (adjusted Risk Ratio(aRR) = 1.97, 95% confidence interval (CI) 1.43–2.72), high DBI polypharmacy (aRR = 1.88; 95% CI 1.36–2.60), oxybutynin (aRR = 1.48; 95% CI 1.01–2.16) and citalopram monotherapy (aRR = 1.96; 95% CI 1.41–2.74), $p < 0.05$) . The odds of developing frailty measured with the clinical frailty index increased with high DBI polypharmacy (adjusted odds ratio (aOR) = 3.13; 95% CI 1.01–9.66) and when measured with the frailty phenotype assessment increased with low DBI polypharmacy (aOR = 4.38, 95% CI 1.40–13.74), high DBI polypharmacy (aOR = 3.43; 95% CI 1.12–10.50) and citalopram monotherapy (aOR = 4.63; 95% CI 1.39–15.54)). No treatment affected time to frailty using either frailty assessment. Analysis of the number of deficits on the frailty index or number of positive criteria on the frailty phenotype allows analysis of rate of change and provides greater sensitivity, while the odds of being frail analysis provided a clinically relevant indicator of whether mice had greater chance of reaching a cut-off for becoming frail with medication exposure than without. Our results are consistent with clinical studies, demonstrating that certain polypharmacy regimens induce frailty, with different relationships observed when using different frailty assessments and analyses.

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PREPRINT

Extensive age-dependent loss of antibody diversity in naturally short-lived turquoise killifish

William J Bradshaw, Michael Poeschla, Aleksandra Placzek, Samuel Kean, Dario Riccardo Valenzano

doi: https://doi.org/10.1101/2020.08.21.261248

Abstract

Aging individuals exhibit a pervasive decline in adaptive immune function, with important implications for health and lifespan. Previous studies have found a pervasive loss of immune-repertoire diversity in human peripheral blood during aging; however, little is known about repertoire aging in other immune compartments, or in species other than humans. Here, we perform the first study of immune-repertoire aging in an emerging model of vertebrate aging, the African turquoise killifish (*Nothobranchius furzeri*). Despite their extremely short lifespans, these killifish exhibit complex and individualized heavy-chain repertoires, with a generative process capable of producing millions of distinct productive sequences. Whole-body killifish repertoires decline rapidly in within-individual diversity with age, while between-individual variability increases. Large, expanded B-cell clones exhibit far greater diversity loss with age than small clones, suggesting important differences in how age affects different B cell populations. The immune repertoires of isolated intestinal samples exhibit especially dramatic age-related diversity loss, related to an elevated prevalence of expanded clones. Lower intestinal repertoire diversity was also associated with transcriptomic signatures of reduced B-cell activity, supporting a functional role for diversity changes in killifish immunosenescence. Our results highlight important differences in systemic vs. organ-specific aging dynamics in the adaptive immune system.

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Association between IGF-1 levels ranges and all-cause mortality: A meta-analysis

The association between IGF-1 levels and mortality in humans is complex with low levels being associated with both low and high mortality. The present meta-analysis investigates this complex relationship between IGF-1 and all-cause mortality in prospective cohort studies. A systematic literature search was conducted in PubMed/MEDLINE, Scopus, and Cochrane Library up to September 2019. Published studies were eligible for the meta-analysis if they had a prospective cohort design, a hazard ratio (HR) and 95% confidence interval (CI) for two or more categories of IGF-1 and were conducted among adults. A random-effects model with a restricted maximum likelihood heterogeneity variance estimator was used to find combined HRs for all-cause mortality. Nineteen studies involving 30,876 participants were included. Meta-analysis of the 19 eligible studies showed that with respect to the low IGF-1 category, higher IGF-1 was not associated with increased risk of all-cause mortality (HR = 0.84, 95% CI = 0.68–1.05). Dose–response analysis revealed a U-shaped relation between IGF-1 and mortality HR. Pooled results comparing low vs. middle IGF-1 showed a significant increase of all-cause mortality (HR = 1.33, 95% CI = 1.14–1.57), as well as comparing high vs. middle IGF-1 categories (HR = 1.23, 95% CI = 1.06–1.44). Finally, we provide data on the association between IGF-1 levels and the intake of proteins, carbohydrates, certain vitamins/minerals, and specific foods. Both high and low levels of IGF-1 increase mortality risk, with a specific 120–160 ng/ml range being associated with the lowest mortality. These findings can explain the apparent controversy related to the association between IGF-1 levels and mortality.

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Characterization of an Aging-Based Diagnostic Gene Signature and Molecular Subtypes With Diverse Immune Infiltrations in Atherosclerosis

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Department of Cardiology, Cangzhou Central Hospital, Cangzhou, China

Objective: Advancing age is a major risk factor of atherosclerosis (AS). Nevertheless, the mechanism underlying this phenomenon remains indistinct. Herein, this study conducted a comprehensive analysis of the biological implications of aging-related genes in AS.

Methods: Gene expression profiles of AS and non-AS samples were curated from the GEO project. Differential expression analysis was adopted for screening AS-specific aging-related genes. LASSO regression analysis was presented for constructing a diagnostic model, and the discriminatory capacity was evaluated with ROC curves. Through consensus clustering analysis, aging-based molecular subtypes were conducted. Immune levels were estimated based on the expression of HLAs, immune checkpoints, and immune cell infiltrations. Key genes were then identified via WGCNA. The effects of CEBPB knockdown on macrophage polarization were examined with western blotting and ELISA. Furthermore, macrophages were exposed to 100 mg/L ox-LDL for 48 h to induce macrophage foam cells. After silencing CEBPB, markers of cholesterol uptake, esterification and hydrolysis, and efflux were detected with western blotting.

Results: This study identified 28 AS-specific aging-related genes. The aging-related gene signature was developed, which could accurately diagnose AS in both the GSE20129 (AUC = 0.898) and GSE43292 (AUC = 0.685) datasets. Based on the expression profiling of AS-specific aging-related genes, two molecular subtypes were clustered, and with diverse immune infiltration features. The molecular subtype–relevant genes were obtained with WGCNA, which were markedly associated with immune activation. Silencing CEBPB triggered anti-inflammatory M2-like polarization and suppressed foam cell formation.

Conclusion: Our findings suggest the critical implications of aging-related genes in diagnosing AS and modulating immune infiltrations.

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Sirt6 regulates lifespan in *Drosophila melanogaster*

Jackson R Taylor [1], Jason G Wood [1], Evan Mizerak [1], Samuel Hinthorn [1], Julianna Liu [1], Matthew Finn [1], Sarah Gordon [1], Louis Zingas [1], Chengyi Chang [1], Mark A Klein [2], John M Denu [2], Vera Gorbunova [3 4], Andrei Seluanov [3 4], Jef D Boeke [5 6 7], John M Sedivy [1], Stephen L Helfand [8]

Affiliations + expand

PMID: 35091469 DOI: 10.1073/pnas.2111176119

Free article

Abstract

Sirt6 is a multifunctional enzyme that regulates diverse cellular processes such as metabolism, DNA repair, and aging. Overexpressing Sirt6 extends lifespan in mice, but the underlying cellular mechanisms are unclear. *Drosophila melanogaster* are an excellent model to study genetic regulation of lifespan; however, despite extensive study in mammals, very little is known about Sirt6 function in flies. Here, we characterized the *Drosophila* ortholog of Sirt6, dSirt6, and examined its role in regulating longevity; dSirt6 is a nuclear and chromatin-associated protein with NAD^+-dependent histone deacetylase activity. *dSirt6* overexpression (OE) in flies produces robust lifespan extension in both sexes, while reducing *dSirt6* levels shortens lifespan. *dSirt6* OE flies have normal food consumption and fertility but increased resistance to oxidative stress and reduced protein synthesis rates. Transcriptomic analyses reveal that *dSirt6* OE reduces expression of genes involved in ribosome biogenesis, including many dMyc target genes. *dSirt6* OE partially rescues many effects of *dMyc* OE, including increased nuclear size, up-regulation of ribosome biogenesis genes, and lifespan shortening. Last, *dMyc* haploinsufficiency does not convey additional lifespan extension to *dSirt6* OE flies, suggesting *dSirt6* OE is upstream of *dMyc* in regulating lifespan. Our results provide insight into the mechanisms by which Sirt6 OE leads to longer lifespan.

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Inhibiting mTTR Aggregation/Fibrillation by a Chaperone-like Hydrophobic Amino Acid-Conjugated SPION

Payam Arghavani, Alireza Badiei, Seyyed Abolghasem Ghadami, Mehran Habibi-Rezaei, Faezeh Moosavi-Movahedi, Ladan Delphi, and Ali Akbar Moosavi-Movahedi*

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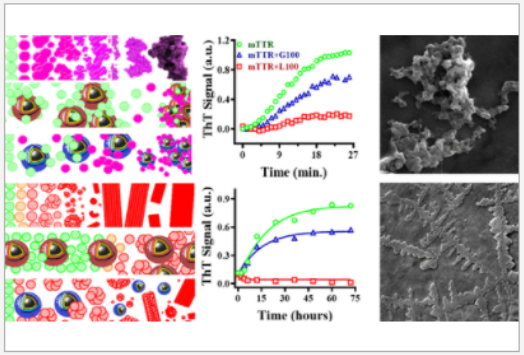
The Journal of Physical Chemistry B

Abstract

Transthyretin (TTR) aggregation via misfolding of a mutant or wild-type protein leads to systemic or partial amyloidosis (ATTR). Here, we utilized variable biophysical assays to characterize two distinct aggregation pathways for mTTR (a synthesized monomer TTR incapable of association into a tetramer) at pH 4.3 and also pH 7.4 with agitation, referred to as mTTR aggregation and fibrillation, respectively. The findings suggest that early-stage conformational changes termed monomer activation here determine the aggregation pathway, resulting in developing either amorphous aggregates or well-organized fibrils. Less packed partially unfolded monomers consisting of more non-regular secondary structures that were rapidly produced via a mildly acidic condition form amorphous aggregates. Meanwhile, more hydrophobic and packed monomers consisting of rearranged β sheets and increased helical content developed well-organized fibrils. Conjugating superparamagnetic iron oxide nanoparticles (SPIONs) with leucine and glutamine (L-SPIONs and G-SPIONs in order) via a trimethoxysilane linker provided the chance to study the effect of hydrophobic/hydrophilic surfaces on mTTR aggregation. The results indicated a powerful inhibitory effect of hydrophobic L-SPIONs on both mTTR aggregation and fibrillation. Monomer depletion was introduced as the governing mechanism for inhibiting mTTR aggregation, while a chaperone-like property of L-SPIONs by maintaining an mTTR native structure and adsorbing oligomers suppressed the progression of further fibril formation.



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PREPRINT

Telomere elongation in the gut extends zebrafish lifespan

Mounir El Maï, Jean-Marie Guigonis, Thierry Pourchet, Da Kang, Jia-Xing Yue, Miguel Godinho Ferreira

doi: https://doi.org/10.1101/2022.01.10.475664

This article is a preprint and has not been certified by peer review [what does this mean?].

Abstract

Telomere shortening is a hallmark of aging and is counteracted by telomerase. The gut is one of the earliest organs to exhibit short telomeres and tissue dysfunction during normal zebrafish aging. This is recapitulated in prematurely aged telomerase mutants (*tert-/-*). Here, we show that gut-specific telomerase activity in *tert-/-* zebrafish prevents premature aging. Induction of telomerase rescues gut senescence and low cell proliferation to wild-type levels, while restoring gut tissue integrity, inflammation, and age-dependent gut microbiota dysbiosis. Remarkably, averting gut dysfunction results in a systemic beneficial impact. Gut-specific telomerase activity rescues premature aging markers in remote organs, such as the reproductive (testes) and hematopoietic (kidney marrow) systems. Functionally, it also rescues age-dependent loss of male fertility and testes atrophy. Finally, we show that gut-specific telomerase activity increases the lifespan of telomerase mutants. Our work demonstrates that delaying telomere shortening in the gut is sufficient to systemically counteract aging in zebrafish.

C. elegans aging research

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PREPRINT

The coupling between healthspan and lifespan in *Caenorhabditis* depends on complex interactions between compound intervention and genetic background

Stephen A. Banse, E. Grace Jackson, Christine A. Sedore, Brian Onken, David Hall, Anna Coleman-Hulbert, Phu Huynh, Theo Garrett, Erik Johnson, Girish Harinath, Delaney Inman, Suzhen Guo, Mackenzie Morshead, Jian Xue, Ron Falkowski, Esteban Chen, Christopher Herrera, Allie J Kirsch, Viviana I. Perez, Max Guo, Gordon J. Lithgow, Monica Driscoll, Patrick C. Phillips

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Abstract

Aging is characterized by declining health that results in decreased neuromuscular function and cellular resilience. The relationship between lifespan and health, and the influence of genetic background on that relationship, has important implications in the development of anti-aging interventions. Here we combined survival under thermal and oxidative stress with swimming performance, to evaluate health effects across a nematode genetic diversity panel for three compounds previously studied in the *Caenorhabditis* Intervention Testing Program – NP1, propyl gallate, and resveratrol. We show that oxidative stress resistance and thermotolerance vary with compound intervention, genetic background, and age. The effects of tested compounds on swimming locomotion, in contrast, are largely species-specific. Additionally, thermotolerance, but not oxidative stress or swimming ability, correlates with lifespan. Our results demonstrate the importance of assessing health and lifespan across genetic backgrounds in the effort to identify reproducible aging interventions.

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Online ahead of print.

Novel elasticity measurements reveal C. elegans cuticle stiffens with age and in a long-lived mutant

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Affiliations + expand

PMID: 35065051 DOI: 10.1016/j.bpj.2022.01.013

Abstract

Changes in biomechanical properties have profound impacts on human health. C. elegans might serve as a model for studying the molecular genetics of mammalian tissue decline. Previously, we found that collagens are required for insulin signaling mutants' long lifespan and that overexpression of specific collagens extends wild-type lifespan. However, whether these effects on lifespan are due to mechanical changes during aging has not yet been established. Here, we have developed two novel methods to study the cuticle: we measure mechanical properties of live animals using osmotic shock, and we directly perform the tensile test on isolated cuticles using microfluidic technology. Using these tools, we find that the cuticle, not the muscle, is responsible for changes in the "stretchiness" of C. elegans, and that cuticle stiffness is highly nonlinear and anisotropic. We also found that collagen mutations alter the integrity of the cuticle by significantly changing the elasticity. In addition, aging stiffens the cuticle under mechanical loads beyond the cuticle's healthy stretched state. Measurements of elasticity showed that long-lived daf-2 mutants were considerably better at preventing progressive mechanical changes with age. These tests of C. elegans biophysical properties suggest that the cuticle is responsible for their resilience.

Accumulation of Glycogen and Upregulation of LEA-1 in *C. elegans daf-2(e1370)* Support Stress Resistance, Not Longevity

by Aleksandra Zečić, Ineke Dhondt and Bart P. Braeckman *

DAF-16-dependent activation of a dauer-associated genetic program in the *C. elegans* insulin/IGF-1 *daf-2(e1370)* mutant leads to accumulation of large amounts of glycogen with concomitant upregulation of glycogen synthase, GSY-1. Glycogen is a major storage sugar in *C. elegans* that can be used as a short-term energy source for survival, and possibly as a reservoir for synthesis of a chemical chaperone trehalose. Its role in mitigating anoxia, osmotic and oxidative stress has been demonstrated previously. Furthermore, *daf-2* mutants show increased abundance of the group 3 late embryogenesis abundant protein LEA-1, which has been found to act in synergy with trehalose to exert its protective role against desiccation and heat stress in vitro, and to be essential for desiccation tolerance in *C. elegans* dauer larvae. Here we demonstrate that accumulated glycogen is not required for *daf-2* longevity, but specifically protects against hyperosmotic stress, and serves as an important energy source during starvation. Similarly, *lea-1* does not act to support *daf-2* longevity. Instead, it contributes to increased resistance of *daf-2* mutants to heat, osmotic, and UV stress. In summary, our experimental results suggest that longevity and stress resistance can be uncoupled in IIS longevity mutants. View Full-Text

REVIEWS/COMMENTS/ METHODS/EDITORIALS

Review Article

The annoying flaws of gerontological research

Magomed Khaidakov, Valeria Troshina, Dmitry Menglet, Yusef Yusef & Alexander Plotkin

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Abstract

Gerontological research has accelerated dramatically in the last few decades. However, despite increased public interest, federal funding, an army of researchers, and many notable discoveries and high-impact publications, the goal of achieving even a modest extension of human lifespan seems to be as far away as ever or, at best, remains within the realm of lifestyle and diet optimization efforts. Humanity has already benefited from a lifespan revolution in the first half of the 20th Century, which was brought about by improved sanitation and hygiene, clean water, and our successful war on infectious diseases. Thanks to all these developments, in which gerontologists played no part, our expected lifespan increased by about 40% and our primary causes of death decidedly shifted from extrinsic to intrinsic causality. The next step is not that simple as it implies tackling intrinsic mechanisms of aging, and the lack of working human-specific antiaging solutions likely stems from flawed research strategies.

Meeting Report: Aging Research and Drug Discovery

Aging is the single largest risk factor for most chronic diseases, and thus possesses large socioeconomic interest to continuously aging societies. Consequently, the field of aging research is expanding alongside a growing focus from the industry and investors in aging research. This year's 8th Annual Aging Research and Drug Discovery (ARDD) meeting was organized as a hybrid meeting from August 30th to September 3rd 2021 with more than 130 attendees participating on-site at the Ceremonial Hall at University of Copenhagen, Denmark, and 1800 engaging online. The conference comprised of presentations from 75 speakers focusing on new research in topics including mechanisms of aging and how these can be modulated as well as the use of AI and new standards of practices within aging research. This year, a longevity workshop was included to build stronger connections with the clinical community.

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Clinical Trials Targeting Aging

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The risk of morbidity and mortality increases exponentially with age. Chronic inflammation, accumulation of DNA damage, dysfunctional mitochondria, and increased senescent cell load are factors contributing to this. Mechanistic investigations have revealed specific pathways and processes which, proposedly, cause age-related phenotypes such as frailty, reduced physical resilience, and multi-morbidity. Among promising treatments alleviating the consequences of aging are caloric restriction and pharmacologically targeting longevity pathways such as the mechanistic target of rapamycin (mTOR), sirtuins, and anti-apoptotic pathways in senescent cells. Regulation of these pathways and processes has revealed significant health- and lifespan extending results in animal models. Nevertheless, it remains unclear if similar results translate to humans. A requirement of translation are the development of age- and morbidity associated biomarkers as longitudinal trials are difficult and not feasible, practical, nor ethical when human life span is the endpoint. Current biomarkers and the results of anti-aging intervention studies in humans will be covered within this paper. The future of clinical trials targeting aging may be phase 2 and 3 studies with larger populations if safety and tolerability of investigated medication continues not to be a hurdle for further investigations.

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Age-Dependent Decline of NAD $^{+}$-Universal Truth or Confounded Consensus?

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Affiliations + expand

PMID: 35010977 PMCID: PMC8747183 DOI: 10.3390/nu14010101

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Abstract

Nicotinamide adenine dinucleotide (NAD^+) is an essential molecule involved in various metabolic reactions, acting as an electron donor in the electron transport chain and as a co-factor for NAD^+-dependent enzymes. In the early 2000s, reports that NAD^+ declines with aging introduced the notion that NAD^+ metabolism is globally and progressively impaired with age. Since then, NAD^+ became an attractive target for potential pharmacological therapies aiming to increase NAD^+ levels to promote vitality and protect against age-related diseases. This review summarizes and discusses a collection of studies that report the levels of NAD^+ with aging in different species (i.e., yeast, *C. elegans*, rat, mouse, monkey, and human), to determine whether the notion that overall NAD^+ levels decrease with aging stands true. We find that, despite systematic claims of overall changes in NAD^+ levels with aging, the evidence to support such claims is very limited and often restricted to a single tissue or cell type. This is particularly true in humans, where the development of NAD^+ levels during aging is still poorly characterized. There is a need for much larger, preferably longitudinal, studies to assess how NAD^+ levels develop with aging in various tissues. This will strengthen our conclusions on NAD metabolism during aging and should provide a foundation for better pharmacological targeting of relevant tissues.

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Targeting cellular senescence with senotherapeutics: senolytics and senomorphics

Lei Zhang, Louise E. Pitcher, Vaishali Prahalad, Laura J. Niedernhofer, Paul D. Robbins

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Abstract

The concept of geroscience is that since ageing is the greatest risk factor for many diseases and conditions, targeting the ageing process itself will have the greatest impact on human health. Of the hallmarks of ageing, cellular senescence has emerged as a druggable therapeutic target for extending healthspan in model organisms. Cellular senescence is a cell state of irreversible proliferative arrest driven by different types of stress, including oncogene-induced stress. Many senescent cells (SnCs) develop a senescent-associated secretory phenotype (SASP) comprising pro-inflammatory cytokines, chemokines, proteases, bioactive lipids, inhibitory molecules, extracellular vesicles, metabolites, lipids and other factors, able to promote chronic inflammation and tissue dysfunction. SnCs up-regulate senescent cell anti-apoptotic pathways (SCAPs) that prevent them from dying despite the accumulation of damage to DNA and other organelles. These SCAPs and other pathways altered in SnCs represent therapeutic targets for the development of senotherapeutic drugs that induce selective cell death of SnCs, specifically termed senolytics or suppress markers of senescence, in particular the SASP, termed senomorphics. Here, we review the current state of the development of senolytics and senomorphics for the treatment of age-related diseases and disorders and extension of healthy longevity. In addition, the challenges of documenting senolytic and senomorphic activity in pre-clinical models and the current state of the clinical application of the different senotherapeutics will be discussed.

One-Carbon Metabolism: Pulling the Strings behind Aging and Neurodegeneration

by Eirini Lionaki [1,†], Christina Ploumi [1,2,†] and Nektarios Tavernarakis [1,2,*]

One-carbon metabolism (OCM) is a network of biochemical reactions delivering one-carbon units to various biosynthetic pathways. The folate cycle and methionine cycle are the two key modules of this network that regulate purine and thymidine synthesis, amino acid homeostasis, and epigenetic mechanisms. Intersection with the transsulfuration pathway supports glutathione production and regulation of the cellular redox state. Dietary intake of micronutrients, such as folates and amino acids, directly contributes to OCM, thereby adapting the cellular metabolic state to environmental inputs. The contribution of OCM to cellular proliferation during development and in adult proliferative tissues is well established. Nevertheless, accumulating evidence reveals the pivotal role of OCM in cellular homeostasis of non-proliferative tissues and in coordination of signaling cascades that regulate energy homeostasis and longevity. In this review, we summarize the current knowledge on OCM and related pathways and discuss how this metabolic network may impact longevity and neurodegeneration across species. View Full-Text

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The Mechanism of Stem Cell Aging

Liangyu Mi, Junping Hu, Na Li, Jinfang Gao, Rongxiu Huo, Xinyue Peng, Na Zhang, Ying Liu, Hanxi Zhao, Ruiling Liu, Liyun Zhang & Ke Xu

Stem Cell Reviews and Reports (2022) | Cite this article

Abstract

Stem cells have self-renewal ability and multi-directional differentiation potential. They have tissue repair capabilities and are essential for maintaining the tissue homeostasis. The depletion of stem cells is closely related to the occurrence of body aging and aging-related diseases. Therefore, revealing the molecular mechanisms of stem cell aging will set new directions for the therapeutic application of stem cells, the study of aging mechanisms, and the prevention and treatment of aging-related diseases. This review comprehensively describes the molecular mechanisms related to stem cell aging and provides the basis for further investigations aimed at developing new anti-stem cell aging strategies and promoting the clinical application of stem cells.

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Physiological hormesis and hormetins in biogerontology

Suresh I.S. Rattan ✉

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https://doi.org/10.1016/j.cotox.2022.01.001

Abstract

Research on the biology of aging and possibilities of interventions has gained a significant push forward by incorporating the concept of mild stress-induced physiological hormesis. Mild stress induced-activation of adaptive and protective pathways in cells and organisms has numerous health-promoting, aging-modulatory and lifespan-extending effects. Moderate and repeated physical exercise is the paradigm for physiological hormesis. Molecular mechanisms for the action of hormetins comprise a cascade of primary stress response pathways, including oxidative stress response, heat shock response, unfolded protein stress response, autophagy, DNA damage response, inflammatory response and sirtuin activation response. Hormetin-based strengthening of the organismic ability of homeodynamics or dynamic homeostasis is a promising holistic approach towards health maintenance, recovery and promotion for healthy aging and longevity.

OTHER RESEARCH & REVIEWS

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Experimenter sex modulates mouse biobehavioural and pharmacological responses

Polymnia Georgiou, Panos Zanos, Ta-Chung M. Mou, Xiaoxian An, Danielle M. Gerhard, Dilyan I. Dryanovski, Liam E. Potter, Jaclyn N. Highland, Carleigh E. Jenne, Brent W. Stewart, Katherine Pultorak, Peixiong Yuan, Chris F. Powels, Jacqueline Lovett, Edna F. Pereira, Sarah M. Clark, Leonardo H. Tonelli, Ruin Moaddel, Carlos A. Zarate Jr, Ronald S. Duman, Scott M. Thompson, Todd D. Gould

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Abstract

Differential rodent responses to the sex of human experimenters could have far reaching consequences in preclinical studies. Here, we show that the sex of human experimenters affects mouse behaviours and responses to the rapid-acting antidepressant ketamine and its bioactive metabolite (*2R,6R*)-hydroxynorketamine. We found that mice manifest aversion to human male odours, preference to female odours, and increased susceptibility to stress when handled by male experimenters. This male induced aversion and stress susceptibility is mediated by the activation of brain corticotropin-releasing factor (CRF) neurons projecting from the entorhinal cortex to hippocampal area CA1. We further establish that exposure to male scent prior to ketamine administration activates CRF neurons projecting from the entorhinal cortex to hippocampus, and that CRF is necessary and sufficient for ketamine's *in vivo* and *in vitro* actions. Further understanding of the specific and quantitative contributions of the sex of human experimenters to different experimental outcomes in rodents may lead not only to reduced heterogeneity between studies, but also increased capability to uncover novel biological mechanisms.